RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-74 were initially filed. Claims 33-74 have been withdrawn from consideration as directed to non-elected subject matter. Claim 3 was canceled without prejudice or disclaimer in the previous response. Claim 1 has been amended herein. No new matter is added by the amendments. Claims 1-2 and 4-32 are currently pending in the application and presented herein for reconsideration.

B. Rejection Under 35 U.S.C. §112, Second Paragraph

The Action rejects claims 1-2 and 4-32 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out the subject matter which Applicant regards as the invention. In particular, the Action asserts that the meaning of the term "capable of" cannot be ascertained in claims 1-2 and 4-32.

In response, Applicants note that the recited term has been deleted in claim 1 in order to advance the prosecution of the case. The amendment does not narrow the scope of the claims. Specifically, the current claim limitations were inherent in "capable of" as it was used in the original claims. Thus Applicants do not disclaim any subject matter through the amendment. It is believed that the rejection is moot in light of the amendment.

In view of the foregoing, removal of the rejection is respectfully requested.

C. Rejection Under 35 U.S.C. §102

The Action rejects claims 1, 5-9, 14-16, 18-21 and 29 under 35 U.S.C. §102(e) as allegedly anticipated by Hultgren *et al.* (US Patent No. 6,001,823). Applicants respectfully

traverse as the cited reference does not teach or suggest all of the claim limitations as is fully demonstrated below.

Current claim 1 of the instant case, upon which each of the remaining rejected claims depends, reads as follows:

> 1. (Currently amended) A method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein that binds a target ligand comprising the steps of:
>
> (a) providing a Gram negative bacterium comprising a nucleic acid sequence encoding a candidate binding protein, wherein said binding protein is expressed in soluble form in the periplasm of said bacterium;
>
> (b) contacting said bacterium with a labeled ligand that diffuses into said periplasm; and
>
> (c) selecting said bacterium based on the presence of said labeled ligand within the periplasm, wherein said ligand and said candidate binding protein are bound in said bacterium.

In contrast to this method, the Hultgren patent provides a method for identifying drugs which, through interaction with periplasmic molecular chaperones, inhibit the assembly of pili in bacteria. See Abstract. However, neither this nor other embodiments of Hultgren et al. teach "selecting said bacterium based on the presence of said labeled ligand within the periplasm, wherein said ligand and said candidate binding protein are bound in said bacterium," as recited in step (c) of claim 1.

The Action asserts, for example, that Hultgren *et al.* teach selection of bacteria based on periplasmic chaperone/pilus subunit binding interactions, thereby teaching the claimed method step of selecting a bacterium. For example, it is stated that Hultgren "teaches a method of obtaining a bacterium as recited in the claimed method" and achieves this by "interaction of a molecular (periplasmic) chaperone with a binding site which is involved in the binding of pilus subunits during transport of these pilus subunits through the periplasmic space (column 8)."

Further it is stated that Hultgren teach that "the periplasmic chaperone being bound to the pilus subunit may be labeled by means of an labeled ligand (column 11-12)" and that Hultgren "teach that bacterium are selected based on the periplasmic chaperone/pilus subunit binding interactions (column 12-14)" and that selection of a bacterium is taught. As illustrated below, however, none of these asserted teachings of Hultgren show or suggest selection of a bacterium based on the presence of a labeled ligand within the periplasm as required by the claims.

Hultgren relates to a fundamentally different method than the claimed method and accordingly teaches different steps. Hultgren relates to "methods for the treatment and/or prophylaxis of diseases caused by tissue-adhering bacteria" in which drugs are identified that interact with periplasmic molecular chaperones and thereby inhibit assembly of pili and diminish infectivity. See Abstract of Hultgren. The cited portions and remainder of the Hultgren reference relate to this problem and include methods for identifying substances that interfere with pili formation. In no case does this teach selecting a bacterium based on the presence of a labeled ligand in the periplasm as in the current claims. This is likely at least in part because there would be no benefit of attempting to do so in the method of Hultgren. The Hultgren technique involves interacting an external "substance"/candidate drug with a "molecular chaperone" produced by the bacterium to obtain an interference with pili formation and the associated reduction in infectivity. See. col. 14, lines 17-45. Hultgren define the "molecular chaperone" as follows:

> By the term "molecular chaperone" is meant a molecule which in living cells has the responsibility of binding to peptides in order to mature the peptides in a number of ways. Many molecular chaperones are involved in the process of folding of peptides into their native conformation whereas other molecular chaperones are involved in the process of export out of or import into the cell of peptides. Specialized molecular chaperones are "periplasmic chaperones", which are bacterial molecular chaperones exerting

> their main actions in the "periplasmic space" (the space between the inner and outer bacterial membrane). Periplasmic chaperones are involved in the process of correct assembly of intact pili. When used herein, the simple term "chaperone" designates a molecular, periplasmic chaperone if nothing else is indicated.

Col. 5, l.59 – Col. 6, l. 6.

The assays described by Hultgren relate to testing an applied "substance" that interacts with this molecular chaperone and thus can interfere with the assembly of pili and have an antibacterial effect. See Abstract. Selection of a bacterium would not further this goal because the bacterium naturally produces the molecular chaperone. The bacterium itself would thus be of no further use because the bacterium in this method is not different from the other bacteria in the assay. It is the "substance" that is selected, not the bacterium, because the substance has antibacterial activity. This is evidenced by the intent to use the molecular chaperone as a target of a therapeutic obtained by the Hultgren method in the treatment of bacterial infections. In contrast, step (c) of claim 1 of the current invention allows one of skill in the art to select a bacterium containing a nucleic acid sequence encoding a candidate binding protein having affinity ligand in question from others that do not contain the sequence. The nucleic acid can then, for example, be isolated from the selected bacterium and used to produce any desired quantity of the newly identified binding protein.

The distinction is illustrated in the sections cited in the Action. For example, Column 6 is cited as teaching that various *in vitro* assays such as microlorimetric or radioimmunoassays could be used, and column 12 is cited as teaching that labeled chaperones, substances and antibodies may be used that are fluorescently labeled. However, such ***in vitro*** techniques do not teach or suggest selection of a ***bacterium*** based on the presence of a labeled ***in the periplasm of the bacterium***. Column 12, for example, relates to studies in which bound molecular chaperones are separated by ultracentrifugation and/or chaperones or substance are immobilized (see col. 12,

lines 5-48 and "step 1" in col. 10, l. 13-63). This therefore involves use of a bacterial lysate rather than selection of a bacterium. With regard to "step 2" this involves the determination of the growth rate of a bacteria or the reduced adherence of bacteria to cells or a synthetic surface. Col. 12, l. 49-67. The lysing and centrifugation of bacterial lysate and application of a candidate substance to bacterial cultures or measurement of the growth rate and tissue adherence of treated bacteria in no way equates to selection of a bacterium based on the presence of a labeled ligand in the bacterium.

Hultgren *et al.* also mentions the use of a fluorescently labeled pilus subunit variant to quantitatively determine the effect of a candidate substance on pilus subunit and periplasmic molecular chaperone binding. (column 14, lines 20-58). However, this step describes ***in vitro*** assays similar to ELISA, involving only protein preparations rather than bacterial cells. (see step (1), column 10, lines 13-63, discussing immobilized and soluble protein; example 10, columns 85-86, 88). Specifically, it is stated that the method is a variation of example 10, which in relevant part refers to ELISA-like assays for quantitative determination of chaperone binding.

Therefore, ***selection of a bacterial cell*** based on the presence of a labeled ligand as required by the claims is not taught or suggested by the prior art. Even if it was assumed that Hultgren discloses an assay measuring the binding between a fluorescently labeled protein and a periplasmic protein in live cells, which Applicant does not concede, it still fails to describe the ***selection*** of a bacterium on the basis of a labeled ligand bound to a binding protein in the bacterial periplasm. Rather, Hultgren *et al.* describe determining and comparing differences in fluorescence between differently treated samples. All of the teachings of Hultgren referred to by the Action therefore involve bacterial lysates or the measurement of physiological responses to treatment with candidate substances. In sum, there is no basis for concluding that this step is

taught or suggested by Hultgren and no justification for concluding otherwise has been provided in the Action.

Findings of fact and conclusions of law by the U.S. Patent and Trademark Office must be supported by "substantial evidence" within the record pursuant to the Administrative Procedure Act ("APA"). *See In re Gartside*, 203 F.3d 1305, 1314-15 (Fed. Cir. 2000); 5 U.S.C. § 706(A), (E), 1994; *see also In re Zurko*, 59 USPQ 2d 1693 (Fed. Cir. 2001). Thus, an Examiner's position must be supported by more than a mere statement that prior art anticipates a claim. Here, no such support for the rejection has been provided and Applicants have affirmatively demonstrated that no such justification exists.

It is the burden of the Office to state with clarity the basis of the rejection. *In Re Lee*, 277 F.3d 1338, 1344-45 (Fed. Cir. 2002). An anticipating reference "must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972). In the instant case, there has been no showing that all elements of the invention have been taught, let alone suggested in combination. Nonetheless, the rejection concludes that the invention is taught by the prior art. It therefore appears that common knowledge, or a "gist of the invention" type approach is being used to support the rejection. This approach is expressly contrary to Federal Circuit caselaw. *Id.* Therefore, if the rejection is maintained, Applicants respectfully request that an affidavit be provided pursuant to 37 C.F.R. §1.104(d) setting forth with clarity the basis for the instant rejection with regard to all claim elements allegedly found in the prior art.

In view of the foregoing, removal of the rejection is respectfully requested.

D. **Rejection Under the Judicially Created Doctrine of Obviousness-Type Double Patenting**

The Action rejects the claims under the judicially-created doctrine of obviousness-type double patenting over copending Application No. 10/620,278. In response, Applicants note that a terminal disclaimer will be filed over the relevant application upon an indication that the claims are otherwise allowable. Removal of the rejections is thus respectfully requested.

E. **Request for Timely Prosecution of the Case**

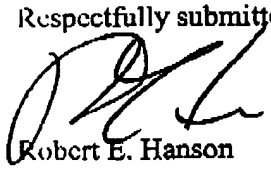
Applicants respectfully note that this is the sixth Office Action received in the case. No adequate basis for rejecting the case has been presented to date and Applicants have fully demonstrated herein and in the previous responses that no such basis exists. The delay in prosecution is unfair to the Applicants, serves no statutory basis in the Patent Laws, and is contrary to MPEP §§707.02 and 707.07, which caution against piecemeal examination. Advancement of the prosecution of the case in as timely a manner as is possible is thus respectfully requested.

Applicants additionally note that the current case will be pending for five years as of October 27, 2005. It is therefore requested that the case be made special no later than as of date pursuant to MPEP §707.02.

F. **Conclusion**

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. The examiner is invited to contact the undersigned at (512) 536-3085 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



Robert E. Hanson
Reg. No. 42,628
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3085

Date: August 16, 2005